Group. Why we need large, simple studies of the clinical examination: the problem and a proposed solution. *Lancet* 1999;354:1721-4.
2 Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6.
3 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326:41-4.
4 Reid MC, Lachs MS, Feinstein A. Use of methodological standards in diagnostic test research. *JAMA* 1995;274:645-51.
5 Arroll B, Schechter MT, Sheps SB. The assessment of diagnostic tests: a comparison of medical literature in 1982 and 1985. *J Gen Intern Med* 1988;3:443-7.
6 Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomised trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
7 Moher D, Jones A, Lepage L, for the CONSORT group. Use of the CONSORT statement and quality of reports of randomised trials. A comparative before-and-after evaluation. *JAMA* 2001;285:1992-5.
8 Devereaux PJ, Manns BJ, Ghali WA, Quan H, Guyatt GH. The reporting of methodological factors in randomised controlled trials and the association with a journal policy to promote adherence to the Consolidated Standards of Reporting Trials (CONSORT) checklist. *Control Clin Trials* 2002;23:380-8.
9 Haynes RB. More informative abstracts: current status and evaluation. *J Clin Epidemiol* 1993;46:595-7.

Contraindications to the use of metformin

Evidence suggests that it is time to amend the list

According to the United Kingdom prospective diabetes study, patients with type 2 diabetes randomised to intensive treatment with metformin, sulphonylurea, or insulin had similar degrees of glycaemic control and significantly reduced microvascular end points.[1] The study showed that the use of metformin in obese patients reduced cardiovascular events. The group treated with metformin had no hypoglycaemia and less weight gain. Treatment with metformin rather than diet alone produced a significant reduction in relative risk in all cause mortality (36%, P=0.011), diabetes related deaths (42%, P=0.017), any diabetes related end point (32%, P=0.0023), and myocardial infarction (39%, P=0.01). Metformin is the only oral hypoglycaemic agent proved to reduce cardiovascular risk and is now recognised as the treatment of choice in overweight patients with type 2 diabetes.

Lactic acidosis associated with metformin is a rare condition with an estimated prevalence of one to five cases per 100 000.[2] Although classically lactic acidosis associated with metformin has been thought of as lactic acidosis secondary to accumulation of metformin, the evidence for this is poor.

Metformin does not affect lactate concentrations in patients with type 2 diabetes,[3] is excreted solely through the kidney, and has a short half life—accumulation of metformin therefore rarely occurs in the absence of advanced renal failure.[4] Accumulation of metformin alone is rarely reported as a cause of lactic acidosis, and tissue hypoxia acting as a "trigger" is found in most instances. Accumulation of metformin does not correlate with lactate concentrations or mortality. Mortality is predicted by the severity of underlying hypoxia.[5] Metformin should therefore be discontinued when tissue hypoxia is suspected.

A recent review of cases of lactic acidosis associated with metformin, which was published between May 1995 and January 2000, concluded that no mortality was associated with metformin alone.[6] Another study noted that the rates of lactic acidosis in the United States before the approval of metformin were no different from the rates observed in users of metformin.[7] A Cochrane systematic review concluded that treatment with metformin was not associated with an increased risk of lactic acidosis.[8]

If adherence to the published contraindications, all of which relate to the feared risk of lactic acidosis, were to be strict, metformin would, or rather should, be seldom prescribed at all. The *British National Formulary* says that any predisposition to lactic acidosis is a contraindication (http://bnf.org/). As diabetes itself is a predisposition to accumulation of lactate,[3] should we stop using the drug altogether in the treatment of diabetes? The *BNF* and other publications also use the terms "renal or hepatic impairment." These terms are vague and therefore unhelpful.

The DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study suggests that treatment with insulin would be the treatment of choice immediately after acute myocardial infarction, but after this no apparent reason exists why metformin should not be reinstated.[9] The withdrawal of metformin in stable chronic heart failure has been questioned as it may have an adverse effect on glycaemic control.[10]

In the United Kingdom it has been shown that doctors tend not to comply with these contraindications. In Southampton 54% of 89 patients treated with metformin had a published contraindication.[11] In Dundee recent analysis of 1847 patients treated with metformin showed that 24.5% (452) had a contraindication to metformin.[12]

Suggested revised contraindications and guidelines for withdrawing metformin

- Stop if serum concentration of creatinine is higher than 150 micromols/l.*
- Withdraw during periods of suspected tissue hypoxia (for example, due to myocardial infarction, sepsis).
- Withdraw for three days after contrast medium containing iodine has been given, and start treatment with metformin only after renal function has been checked.
- Withdraw two days before general anaesthesia and reinstate when renal function is stable.

*Any concentration of creatinine that is chosen as a cut-off point for renal failure will be arbitrary in view of individual patients' muscle mass and protein turnover, and caution should therefore be used in prescribing metformin for elderly patients. This at least avoids non-specific and unhelpful terms such as renal insufficiency or renal impairment.

BMJ 2003;326:4–5

Although circumstantial evidence shows that treatment with metformin may be linked with lactic acidosis, no causal relation has been proved. Metformin is proved to reduce plasma glucose and complications of diabetes. Uniquely, it is the only hypoglycaemic agent to date that has been shown to reduce the macrovascular complications of diabetes.[1] Current published guidelines vary and may limit the use of metformin and cause confusion among doctors. It is essential that the benefits of treatment with metformin be made available to as wide a group of appropriate patients as possible without laying prescribers open to criticism or litigation in the event of concomitant lactic acidosis. A simplified and pragmatic set of guidelines should be adopted, stressing the importance of renal clearance of metformin and withdrawal of metformin in patients with tissue hypoxia.

As metformin is the only oral hypoglycaemic agent proved to reduce cardiovascular mortality, its use should be as widespread as possible in type 2 diabetes. We hope that these suggested guidelines are less ambiguous than current ones and prevent the current situation of many clinicians, who are having to ignore written contraindications in order to maximise the use of metformin appropriately.

G C Jones *consultant physician*
(greg.jones@northglasgow.scot.nhs.uk)

J P Macklin *senior house officer*

Department of Diabetes, Gartnavel General Hospital, Glasgow G12 0YN

W D Alexander *consultant physician*

Diabetes Centre, Western General Hospital, Edinburgh EH4 2XU

Competing interests: None declared.

1 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
2 Brown JB, Pedula, MS, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 1998;21:1659-63.
3 Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in non insulin-dependent diabetes mellitus. *J Clin Endocrinol Metabol* 1996;81:4059-67.
4 Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 1996;30:359-71.
5 Lalau JD, Lacroix C, De Cagny B, Fournier A. Metformin associated lactic acidosis in diabetic patients with acute renal failure. A critical analysis of its pathogenesis and prognosis. *Nephrol Dial Transplant* 1994;9:126-9.
6 Lalau JD, Race JM. Lactic acidosis in metformin therapy: searching for a link with metformin in reports of "metformin associated lactic acidosis". *Diabetes Obes Metabol* 2001;3:195-201.
7 Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998;338:265-6.
8 Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2002;(2):CD002967.
9 Malmberg K, for the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997;314:1512-5.
10 Hart SP, Walker JD. Is metformin contra-indicated in diabetic patients with chronic stable heart failure? *Pract Diabetes Int* 1996;13:18-20.
11 Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 1997;20:925-8.
12 Emslie-Smith AM, Boyle DIR, Evans JMM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with type 2 diabetes—a population-based study of adherence to prescribing guidelines. *Diabet Med* 2001;18:483-8.

Evidence based policy making

Impact on health inequalities still needs to be assessed

Powerful, rich, and well educated people tend to live longer and healthier lives than their less advantaged counterparts. These socioeconomic inequalities in health have been observed in a range of societies—developed, developing, market led, welfare state, and communist. Their expression, however, may vary according to how the particular society is stratified—for example, by income or wealth in the United States, by social class in the United Kingdom, or by education in Europe. They occur across a wide range of causes of death and types of illness, have been observed since accurate statistics were first available, and seem to have been increasing.[1]

Several governments have recently proposed strategies to reduce socioeconomic inequalities in health.[2–5] An issue rendering strategy development in this field difficult is that, although a lot of information is available about the magnitude and causes of socioeconomic inequalities in health, rather less information is available about the effectiveness of policies in reducing them.[6] The recent Cross-Cutting review in England noted that intervention research is scanty compared with the much larger body of observational evidence that describes inequalities.[5] This is shown by the fact that the review contains six boxed lists, containing between them 50 examples of inequalities in health and only one box with rather general, and mainly process related, recommendations for successful interventions.[5]

Unfortunately, knowing the prevalence and causes of a health problem does not always tell us the most effective way to reduce it. For example, knowing the links between smoking and lung cancer, child labour and poor health, or HIV and AIDS may help provide goals such as reducing smoking, child labour, or risky sex, but does not necessarily tell us how to achieve these goals. As is apparent from several fields, the plausibility of proposed interventions is no guarantee of their actual efficacy.[7] Thus anyone wanting to reduce inequalities in health is faced with a lack of information about what actions would be most successful.

Why do we lack this information? Firstly, many studies, such as a recent randomised controlled trial of supplementation with antioxidant vitamin to prevent heart disease and cancer,[8] do not report whether

BMJ 2003;326:5–6